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CITMA WHITE PAPER: PROPOSED STREAMLINED PATHWAYS FOR DEEMED PRODUCTS

1. Abbreviated PMTAs for ENDS Products - Framework

Congress designed the PMTA process for premarket review of "new" forms of traditional tobacco products. Thus, this pathway must be modified for products such as ENDS that fall on the opposite end of the risk continuum from combustible products and that Congress could not have contemplated when crafting the Family Smoking Prevention and Tobacco Control Act. FDA should provide additional flexibility with respect to PMTAs for ENDS products, while still appropriately protecting the public health, by establishing an abbreviated PMTA pathway for categories of products on the lower-risk end of the continuum. Because the Federal Food, Drug, and Cosmetic Act (FFDCA) provides FDA with broad discretion to determine if a PMTA, "along with any other information before the Secretary with respect to such tobacco product," demonstrates that "permitting such tobacco product to be marketed would be appropriate for the protection of the public health,"[1] FDA has the statutory authority to implement abbreviated PMTA procedures for certain categories of tobacco products.

This abbreviated PMTA pathway should consist of a "provisional approval" based on certain parameters, coupled with marketing conditions and postmarketing commitments. Such a regulatory approach was proposed by Dr. David Abrams early in 2014.[2] It should also provide for priority meetings with the Agency to discuss the required contents of the abbreviated PMTA, a rolling review of submissions, and a shorter time clock for review of applications. A failure to comply with the conditions of approval or any postmarketing commitments could result in enforcement action or withdrawal of provisional approval. In addition, FDA may withdraw approval of an abbreviated PMTA if it determines that, based on postmarketing data or other evidence, the product is no longer appropriate for the protection of the public health.

For instance, an abbreviated PMTA for an ENDS product could consist of the following:

1. Full reports of any investigations of health risks related to the new product or a comparable product in the possession of the applicant at the timing of filing;
2. A full statement of all components, ingredients, additives, and properties, and of the principle or principles of operation;
3. A full description of methods of manufacturing and processing;
4. Results of constituent testing of liquid and vapor (consistent with applicable guidance from FDA), as applicable;
5. Samples of the product and its components;
6. Any marketing data or plans in the possession of the applicant for the product; and
7. Specimens of current labeling and promotional materials and those intended for dissemination or publication within 120 days following issuance of a PMTA order.

[1] 21 U.S.C. § 387j(c)(2).

[2] Abrams DB. Promise and peril of e-cigarettes: can disruptive technology make cigarettes obsolete? JAMA 2014;311:135-136.

FDA could condition the issuance of a marketing order on the following:

1. A demonstration that the product meets certain specified constituent testing and/or other manufacturing standards;
2. Compliance with any existing flavor standards developed by industry or the Agency; and
3. A commitment to:
    a. Submit samples of all promotional materials at least 30 days prior to the intended time of dissemination of the labeling or initial publication of the advertisement;
    b. Conduct certain postmarket surveillance and report postmarketing data at set time intervals as directed by FDA for at least three years; and
    c. Comply with reasonable conditions of approval on the labeling of the product as directed by FDA.

To receive provisional approval, an abbreviated PMTA application would include constituent testing of the liquid and vapor, but applicants would ***not*** be required to conduct new clinical or nonclinical studies on the new product that is the subject of the application, including in vitro or in vivo toxicology studies, abuse liability evaluations, carcinogenicity studies, use pattern/topography evaluations, clinical pharmacology investigations, human factors research, or studies comparing the new product to other tobacco products in terms of health effects.

Likewise, an abbreviated PMTA would ***not*** be required to contain consumer use studies, including those relating to the likelihood that consumers will adopt the new product and then switch to other tobacco products, the likelihood of consumers using the new product in conjunction with other tobacco products, or the likelihood of consumers switching to the new product instead of ceasing tobacco product use or using an FDA-approved tobacco cessation product. Abbreviated PMTA applicants would also ***not*** be required to study the likelihood that nonusers, including youth, may initiate with the new product. Rather, these consumer use and behavior issues will be explored via postmarket surveillance and data.

FDA should additionally provide for the flexibility to bundle multiple, related products into a single PMTA submission (e.g., various nicotine strengths and flavors, various size and package configurations). Furthermore, prior to requiring the submission of PMTAs for deemed products, FDA should, via guidance or regulation, establish a process for modifications to PMTA-approved ENDS products. FDA might use as a model its procedures for making changes to drug products approved under new drug applications (NDAs) or abbreviated NDAs.[3] As in the drug context, FDA should designate categories of changes to PMTA-approved ENDS products that may be made without prior FDA approval.

These alternative regulatory approaches would enable products that present lower relative risk such as ENDS to stay on the market subject to certain conditions while helping to generate the data and information needed for FDA to fully confirm the products' impact on the public health. They would also set expectations that smaller ENDS companies could at least potentially meet, while still satisfying FDA's regulatory objectives, and allow for continued innovation. In that

[3] *See* 21 C.F.R. § 314.70.

regard, before requiring the filing of abbreviated marketing submissions for currently marketed ENDS products, FDA should finalize and implement this policy sufficiently in advance (no less than one year) of the filing deadline.

2. Develop Standard Reference Products for Use as "Predicates" in SE Process

A large percentage of small deemed combustible product (cigar, pipe tobacco) manufacturers entered the market after February 2007. All ENDS product manufacturers and importers entered the market after February 2007. Accordingly, these companies do not have access to adequate information about a 2007 predicate product. In order to enable these small manufacturers to survive, FDA should establish standardized reference products for each sub-category (e.g., larger ring gauge cigars, filtered cigars, cigarillos, pipe tobacco, and hookah, as well as ENDS products, each with and without flavors, in various packaging configurations) to which manufacturers could compare their products in the context of an SE report in lieu of a grandfathered product. The combustible reference products could be based on typical products marketed in 2007 and information regarding those products could be obtained by the component suppliers. The ENDS reference product could be developed in a process similar to the National Institute on Drug Abuse (NIDA) of the National Institutes of Health (NIH) process to develop a standardized electronic cigarette for use in clinical research. *See* SBIR Topic 156, Solicitation Number: N43DA-15-8921 (May 29, 2014). *Available at* https://www.fbo.gov/index?s=opportunity&mode=form&id=9d121f4da6d8ecec8e6e668c10050947&tab=core&tab mode=list&. FDA could publish the specifications for this reference product for use by manufacturers as a surrogate "predicate."

We acknowledge that FDA appears to have rejected a similar approach in the context of cigarettes. See, e.g., Technical Project Lead (TPL) Review for 4 R.J. Reynolds Tobacco Company products (SE0000276, SE0000277, SE000278, SE0000281) (9/11/15) (FDA advised RJR that its SE reports were deficient because they cited as a predicate "a composite of all cigarettes commercially marketed in the United States as of February 15, 2007" and therefore did not "fully identify the predicate product (i.e., how the predicate tobacco product is uniquely identified for a consumer such as brand, subbrand, size, quantity, and packaging).") We submit that because many more years have now passed since the 2007 grandfather date, FDA must reconsider this overly strict interpretation of the Act in the context of newly deemed products such as cigars, pipe tobacco, hookah and ENDS products. Moreover, rather than citing a "composite" of marketed products, this proposal envisions that FDA itself would establish the specifications for the standardized predicates. This approach would benefit public health because the Agency would have control over the specifications for the "predicate" reference product and therefore would be setting the base standard for comparison.

FDA has the statutory authority to establish a "predicate" product for the purposes of SE reports. Section 910 of the FFDCA states that the term "substantially equivalent" means "that the Secretary by order has found that the tobacco product – (i) has the same characteristics as the predicate tobacco product; or (ii) has different characteristics and the information submitted contains information … that demonstrates that it is not appropriate to regulate the product under this section because the product does not raise different questions of public health." Importantly, however, the term "predicate tobacco product" is not defined in the FFDCA.

Section 905(j) provides that a product that was not commercially marketed in the United States as of February 15, 2007, must submit a report demonstrating that the product is SE to a product commercially marketed in the U.S. as of February 15, 2007, or to a product that the Secretary has previously determined, pursuant to Section 910, is "substantially equivalent." Based on this latter phrase, FDA could establish a standardized "predicate tobacco product" and determine that all reasonably identical products are "substantially equivalent" to this standardized product because they have the same or substantially similar characteristics. For products that are not reasonably identical to the standardized predicate, an SE report would need to demonstrate that the new tobacco product does not raise different questions of public health than the products that have been determined by FDA to be substantially equivalent to (in this case, reasonably identical to) the standardized predicate product developed by the Agency.

Indeed, there is precedent for FDA approaching an overwhelming regulatory review task like this one in a very analogous way: the OTC Review. In 1962, Congress amended the FFDCA to add a requirement that drugs be shown to be effective as well as safe. In light of this new efficacy requirement, FDA had to determine how to regulate the hundreds of thousands of drugs that were already on the market and were not approved under an NDA that demonstrated both safety and effectiveness. For over-the-counter (OTC) drugs, of which there were an estimated 100,000 to 500,000 on the market, FDA decided in 1972 to establish the OTC monograph system, or OTC Review, to review the safety and effectiveness of OTC drugs by therapeutic category rather than rather than individually. 37 Fed. Reg. 85 (Jan. 5, 1972).

In deciding to proceed in this way, the Agency acknowledged:

> The limited resources of the Food and Drug Administration would be overwhelmed by attempting to review separately the labeling and the data on the safety and effectiveness for each OTC drug now on the market. This would be further complicated by the almost daily growth in the number of drugs being marketed and the changes in formulation and labeling of previously marketed drugs … The prospects of completing a detailed drug-by-drug review of the OTC market in a reasonable time are extremely remote.

37 Fed. Reg. at 86. Of relevance here, FDA also observed:

> Practically all of the thousands of OTC drugs now marketed are compounded from only an estimated 200 active ingredients which are used either alone or in varying combinations. Many thousands of these drugs are readily comparable in that the labeling is similar and the active ingredients are the same, or are essentially the same, but are present in slightly different dosages.

Id.

Likewise, most cigars, pipe tobacco and hookah products on the market contain very similar ingredients and components to one another and most ENDS products on the market contain liquids with similar ingredients and use common delivery device features. Permitting comparison to a standardized predicate product established by FDA would allow the Agency to

review specific information about the product that is the subject of the SE report while comparing it to one singular standard. Like the OTC Review, this would enable the Agency to protect the public health in an efficient manner without bringing the Agency's SE review process to a virtual standstill and/or decimating the marketplace for the smaller industry players.